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Methamphetamine-Associated Congestive Heart Failure: Increasing Prevalence and Relationship of Clinical Outcomes to Continued Use or Abstinence

Sean Sliman[1] · Jill Waalen[2] · David Shaw[1]

Abstract The purpose of this study was to determine the prevalence of methamphetamine-associated congestive heart failure (MAC) and to evaluate the relationship between methamphetamine abuse and EF and functional status over time. A retrospective review of records from 2009 to 2014 was carried out. Prevalence of methamphetamine abuse among all patients admitted with CHF was calculated for each of the 6 years of the study ($n = 141$) and was compared with prevalence of cocaine abuse and alcohol abuse. For patients with two or more admissions during the entire time period, the trajectories of NYHA functional class and EF over time were determined ($n = 58$). MAC has significantly increased from 1.8 to 5.6 % of total CHF patients admitted ($n = 3705$). Among patients who stopped using methamphetamine, NYHA functional class significantly improved, while among patients who continued methamphetamine use, NYHA was significantly worsened ($p < 0.001$). Significantly more patients with improved EF stopped using methamphetamine than continued ($p = 0.05$). There was a significant increase in the prevalence of MAC during the study period for all CHF patients admitted in our hospital system. Continued methamphetamine use is associated with worsening functional status, while cessation of methamphetamine is associated with improvement in functional status.

Keywords Methamphetamine · Cardiomyopathy · Heart failure · Prevalence · Drug abuse

Introduction

Methamphetamine is the most widely manufactured and abused stimulant in the USA [1] and is second to only cannabis as the most widely abused illicit drug worldwide [2]. Currently, the use of methamphetamine is much more common in the Western United States and Hawaii [3]. However, data show that there is a shift towards increased use eastward into the Midwest and South [3, 4]. The widespread use and deleterious effects of methamphetamines make it a growing public health and clinical concern.

Heart failure is accountable for over 1 million hospitalizations, as well as $32 billion in costs, annually in the USA [5, 6]. There is a growing body of evidence for the association of illicit stimulant use, specifically cocaine and methamphetamine, with cardiomyopathy [7–11]. Of patients with self-reported illicit drug use associated with acute decompensated heart failure in a nationwide study from 2004 to 2006, a large majority of patients self-reported cocaine use (96 %), while only 5 % of patients reported methamphetamine use [7]. Despite these nationwide data, the prevalence of acute decompensated heart failure from methamphetamine may also have regional predilection reflecting higher usage in the Western United States.

Although there is an increasing amount of literature on the association between methamphetamine use and cardiomyopathy, there seems to be a lack of data on

✉ David Shaw
Shaw.david@scrippshealth.org

[1] Department of Graduate Medical Education, Scripps Mercy Hospital, 4077 Fifth Avenue, MER-35, San Diego, CA 92103, USA

[2] Department of Molecular and Experimental Medicine, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

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prevalence in the setting of other commonly coexisting etiologies including alcohol, cocaine, coronary artery disease and hypertension. In addition, the effect of continued use or discontinuation of methamphetamine upon EF and functional status over time has not previously been reported in a systematic fashion. Therefore, we sought to describe the prevalence and clinical course of methamphetamine-associated congestive heart failure (MAC) in a large urban community hospital system in southern California over the course of 6 years from 2009 to 2014. We hypothesized that MAC prevalence has increased over the 6-year period and that there exists a temporal relationship between continued use of methamphetamine and deterioration in cardiac function and patient functional status over time.

Materials and Methods

The study took place at a two-campus 684-licensed-bed community hospital, with one campus centrally located in San Diego and another adjacent to the Mexican border, during the time period of January 2009 to December 2014. IRB approval for this study was obtained from the Scripps Office for the Protection of Research Subjects, IRB-15-6569.

Retrospective review of data retrieved from the hospital billing records and electronic medical record was performed in order to first identify appropriate patients and then review subsequent admission data over the time period. All patients with a principal ICD-9 diagnosis code of 428.xx, 402.01, 402.11, 402.91, 404.01,404,03, 404.11, 404.13, 404.91 or 404.93 were counted as CHF admissions. Each patient was counted only once in each year for prevalence data. Patients were defined as having methamphetamine abuse with codes 305.70, 305.71, 305.72, 305.75, 304.40, 304.41, 304.42 or 304.43. They were coded as having cocaine abuse with codes 305.60, 305.61, 305.62, 305.63, 304.20, 304.21, 304.22 or 304.23. They were coded as having alcohol abuse with codes 303.00, 303.01, 303.02, 303.03, 303.90, 303.91, 303.92, 303.93, 305.00, 305.01, 305.02 or 305.03. In situations with abuse of more than one substance, we included each substance in the prevalence data for that substance. Patients who used more than one substance known to be associated with cardiomyopathy, but which included methamphetamine were considered to have methamphetamine-associated congestive heart failure, whether or not they had other potential confounding etiologies of congestive heart failure.

Patient records identified for this study underwent review regarding last use and pattern of abuse of alcohol, cocaine and methamphetamine using the electronic medical records from all clinical notes including ED, history and physical, discharge summary and consult physician notes as well as drug toxicological screens over time. Once identified as a patient of record for this study, all subsequent hospitalizations and ED visits for that patient were reviewed, regardless of admission diagnoses.

The following data elements were determined using all clinical notes described above: age, gender, self-reported race/ethnicity and all dates of admission(s); New York Heart Association functional class, determined on admission by report or deduced from history given; ejection fraction(s) and date(s) of echocardiogram(s); as well as other causes of cardiomyopathy, including coronary artery disease (determined by coronary angiography or noninvasive testing including stress echocardiography or sestamibi nuclear stress testing). For patients with multiple admissions, including admissions without CHF as primary diagnosis, the methamphetamine trajectory, defined as the time course of use, was determined where data were available to identify whether the patient had stopped, continued or had fluctuating use, defined, as intermittent use of methamphetamines with periods of abstinence, then resumed use. Patients with fluctuating use were not included in the data analysis ($n = 4$) as the relative degree of abstinence and use could not be determined. The time course of abuse of cocaine and alcohol was reviewed for the discontinued methamphetamine group as well. Ejection fraction was determined from the stated value in reports of standard echocardiography performed during patient admission. Ejection fraction trajectory, defined as the increase or decrease over time, was determined, when two or more measurements, separated by at least one month, were available. As the accepted SEM of ejection fraction, when estimated by echocardiography, is 7 % [12], $a \geq 15$ % change from previous study was considered as significantly increased or decreased, and when <15 % was considered stable. EF and NYHA functional class were determined from the history and physical reports reviewed for all hospital admissions including those not for exacerbation of CHF. For prevalence data, only one admission was counted for each year in which prevalence was determined. For overall prevalence during the 6 years of the study, each patient was only counted once.

Statistical Methods

Differences in mean age and sex distributions between all patients admitted with acute decompensated heart failure and those admitted with methamphetamine-associated cardiomyopathy were assessed by *t* test and Chi-square test, respectively. If a patient had more than one type of substance abuse, then that patient was counted in the numerator for each specific type of substance abuse. The

percentage of cases of congestive heart failure attributed to a specific type of substance abuse by year (calculated using all cases of congestive heart failure seen in that year as the denominator) was compared across years using the Chi-square test of trend. Associations between methamphetamine trajectory and the outcomes of EF trajectory and, separately, of NYHA trajectory were assessed by the Chi-square test. Agreement between the ejection fraction trajectory and the trajectory of NYHA symptoms as outcomes was assessed using the kappa statistic. p values were considered statistically significant at a two-sided alpha = 0.05. Data were analyzed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

A total of 3705 patients were admitted with a principal admitting diagnosis of congestive heart failure from January 2009 to December 2014. Of these, 141 individuals were identified with the comorbidity of methamphetamine abuse. The demographic and clinical characteristics of the MAC cohort are given in Table 1.

The mean age of the MAC group was significantly younger ($p < 0.001$) at 51.2 (range 21–73; SD ± 9.3) at earliest CHF, compared with mean age of 71.8 (range 21–102; SD ± 15.1) for all CHF patients, including those with and without methamphetamine abuse. Male gender was significantly more prevalent in those with MAC compared with all CHF patients, 79.3 versus 51.3 %, respectively ($p < 0.001$).

The prevalence of MAC significantly increased from 2009 to 2014 ($p < 0.001$). Of all CHF admissions, 1.8 % was attributed to MAC in 2009 compared with 5.58 % in 2014. There was not a significant change in the prevalence of cocaine-associated ($p = 0.23$) or alcohol-associated ($p = 0.18$) congestive heart failure during this same time period as shown in Table 2 and Fig. 1.

A proportion of our patients (13/141 = 9.2 %) presented with heart failure with preserved ejection fraction (EF > 45 %). Of these 13 echocardiogram reports, nine commented on the pulmonary artery (PA) pressure of which seven were elevated, with an average PA pressure of 49.4.

Of the 141 patients in the MAC group, 54 have data for both ejection fraction trajectory and methamphetamine abuse trajectory, excluding those with fluctuating methamphetamine use ($n = 4$). Of these 54, 48.3 % had no other CHF etiology, 20.7 % had a history of coronary artery disease, 19.0 % had a history of alcohol abuse and 6.9 % had a history of other possible etiology including AIDS, end-stage renal disease or obstructive sleep apnea given in Table 1. Of the 30 patients with discontinued methamphetamine use, 93 % (28/30) abstained from all drugs and alcohol, while two patients had continued alcohol abuse. Those with methamphetamine only abuse eventually discontinued use 38.6 % of the time while 27.6 % of patients with concomitant cocaine or alcohol abuse were able to abstain from continued methamphetamine use, which was not statistically significant ($p = 0.35$).

EF trajectory showed a trend toward correlation with methamphetamine use trajectory which does not reach clinical significance ($p = 0.06$), as shown in Table 3 and Fig. 2. The proportion of patients in whom EF improved was significantly higher in those who abstained from methamphetamine when compared to those who continued, 35.3 versus 10.8 %, respectively ($p = 0.05$).

Sixty-one patients have data for both NYHA functional class trajectory and methamphetamine abuse trajectory. The association of NYHA functional class trajectory with methamphetamine trajectory was statistically significant ($p < 0.001$) as shown in Table 4 and Fig. 3.

NYHA class improved in 55.6 % of patients with discontinued methamphetamine trajectory and only 7.7 % in those with continued methamphetamine use. NYHA class worsened in 46.1 % of patients with continued methamphetamine use and only 5.6 % of those with cessation of use. The relationship between methamphetamine use and NYHA functional class remained significant when analyzed controlling for cocaine and alcohol abuse NYHA functional class ($p = 0.0003$). Of those patients with a clear discontinuation date and follow-up, the average time for improvement in functional class was 8 weeks (range 2–12 weeks).

Discussion

Our study, performed in a community hospital in southern California, showed a significant increase in the prevalence of MAC without significant increase in alcohol- or cocaine-associated congestive heart failure over the 6-year study period. A clear association has previously been described between dilated cardiomyopathy and chronic methamphetamine use in the absence of occlusive coronary artery disease in a cohort of 21 patients [11]. In our larger cohort ($n = 141$), other possible etiologies of cardiomyopathy were included as multiple concurrent etiologies of cardiomyopathy are part of the real-world picture. In addition, our results show that NYHA functional class trajectory was significantly associated with methamphetamine trajectory over time. EF trajectory showed a trend toward correlation with methamphetamine use trajectory which does not reach clinical significance. This is the first description in the literature with regard to an association between clinical

Table 1 Descriptive statistics

Characteristic	All in cohort ($n = 141$)		Subjects with data for both EF trajectory and meth trajectory ($n = 58$)	
	Mean (SD) or n (%)	Range	Mean (SD) or n (%)	Range
Current age (years)	52.0 (9.4)	26–78	51.5 (9.9)	26–78
Sex				
Male	112 (79.4)		46 (79.3)	
Female	29 (20.6)		12 (20.7)	
Age at earliest CHF (years)	47.5 (9.6)	21–73	46.2 (10.4)	
Race/ethnicity				
White	67 (42.5)		25 (43.1)	
Black	34 (24.1)		13 (22.4)	
Hispanic	34 (24.1)		18 (31.0)	
Asian	6 (4.3)		2 (3.5)	
Other drugs				
None	76 (53.9)		32 (55.2)	
Alcohol	38 (27.0)		17 (29.3)	
Cocaine	14 (9.9)		4 (6.9)	
Alcohol + cocaine	13 (9.2)		5 (8.6)	
EF trajectory				
Improving (≥15 % change)	16 (11.4)		11 (19.0)	
Stable (<15 % change)	37 (26.2)		27 (46.6)	
Worsening (≥15 % change)	27 (19.2)		20 (34.5)	
NYHA trajectory				
No data	30 (21.3)		11 (19.0)	
Improving	18 (12.8)		9 (15.5)	
Stable	37 (26.2)		23 (39.7)	
Worsening	24 (17.0)		14 (24.1)	
Meth trajectory				
No data	51 (36.2)		–	
Abstaining	30 (21.3)		17 (29.3)	
Continues	56 (39.7)		37 (63.8)	
Fluctuating	4 (2.8)		4 (6.9)	
Other CHF etiologies				
None	68 (48.2)		28 (48.3)	
Coronary artery disease	21 (14.9)		12 (20.7)	
Alcohol	26 (18.4)		11 (19.0)	
Cocaine	7 (5.0)		0	
Polysubstance abuse	10 (7.1)		3 (5.2)	
Other[a]	9 (6.4)		4 (6.9)	
Any meth screen				
Not done	14 (9.9)		3 (5.2)	
Positive	100 (70.9)		47 (81.0)	
Negative	27 (19.2)		8 (13.8)	
EF1 (%) ($n = 141$)	29.9 % (16.4)	6–73 %	31.9 % (17.8)	7–73 %
EF2 (%) ($n = 79$)	30.7 % (18.3)	5–75 %	28.9 % (17.1)	7–74 %
Median time of CHF follow-up (years)	2	0–10	3	0–10

[a] Including OSA, ESRD, HIV/AIDS

Table 2 Substance abuse-associated congestive heart failure by year

Year	All patients	Meth	% Meth*	EtOH	% EtOH^{+}	Cocaine	% Cocaine^{+}
2009	668	12	1.80	35	5.24	6	0.90
2010	710	16	2.25	37	5.21	6	0.85
2011	717	18	2.51	40	5.58	7	0.98
2012	706	27	3.82	40	5.67	6	0.85
2013	751	41	5.46	41	5.46	12	1.60
2014	807	45	5.58	56	6.94	10	1.24

* $p < 0.001$ Chi-square test for trend 2009–2014

$^{+}$ ($p = 0.18$ for EtOH and $p = 0.23$ for cocaine by Chi-square test for trend)

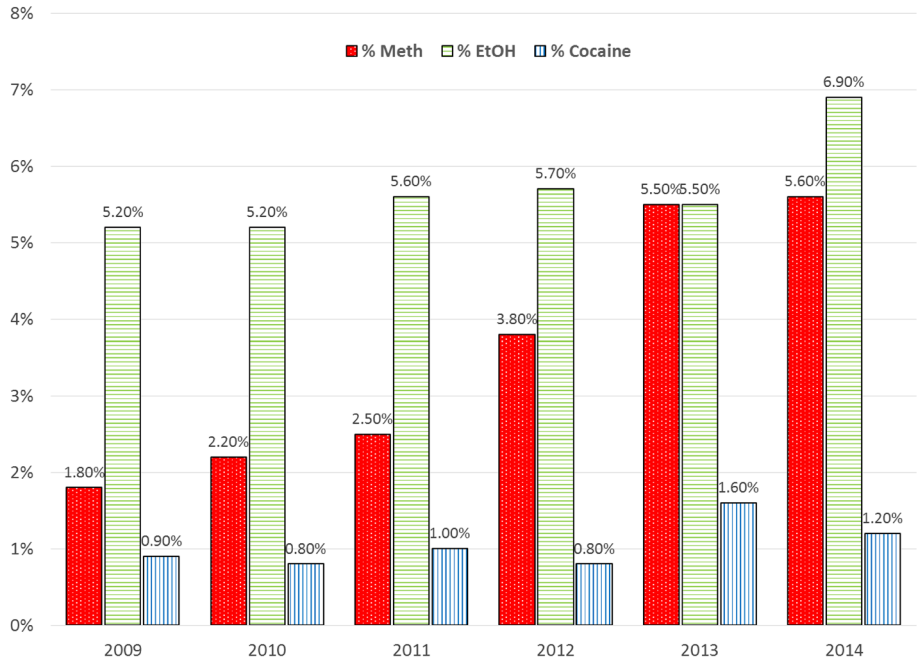

Fig. 1 Patients with substance abuse as percentage of all patients with heart failure admission ($p < 0.001$ for methamphetamine trend; $p = 0.18$ for EtOH and $p = 0.23$ for cocaine)

Table 3 EF trajectory by meth trajectory ($n = 54$ with data for both)

Meth trajectory	EF trajectory *n* (% of row)		
	Improving	Stable	Worsening
Discontinued ($n = 17$)	6 (35.3)	8 (47.1)	3 (17.7)
Continued ($n = 37$)	4 (10.8)	17 (46.0)	16 (43.2)

Overall *p* value (for 2 × 3 table): 0.06 (Fisher's exact test)

p value for comparing % EF trajectory improving by meth trajectory (i.e., 35.3 % EF improved in those with an improving meth trajectory versus 10.8 % EF improved in those with a continued meth trajectory): 0.05 (Fisher's exact test)

p value for comparing % EF trajectory worsening by meth trajectory (i.e., 17.7 % EF worsening in those with improving meth trajectory versus 43.2 % EF worsening in those with a continued meth trajectory): 0.12 (Fisher's exact test)

status and continuation of or abstinence from methamphetamine use confounded by possible noncompliance to standard CHF therapy.

Illicit drug use has risen to almost its highest level in a decade in the USA [2]. Approximately 22.5 million people self-reported using illicit drugs in the month prior to survey [2]. Methamphetamine abuse has traditionally been seen most commonly in Hawaii and in the Western United States. However, there has been a clear increase in abuse spreading eastward [13]. Although there have been reports of methamphetamine use stabilizing, the amount of dependence has clearly risen [14, 15]. Overall national trends of methamphetamine abuse are showing declines; however, use continues to exhibit regional variability [16]. In San Diego County, methamphetamine indicators were trending upward with primary methamphetamine treatment admissions reaching 29 % [17] as well as the number and rate of overdose-related deaths [17]. During this same time period, the amount of crack/cocaine use has leveled off after showing recent decline [17]. Overall, amphetamine-like substances, including methamphetamine, are the fastest rising drugs of abuse worldwide [18]. There is a growing body of evidence

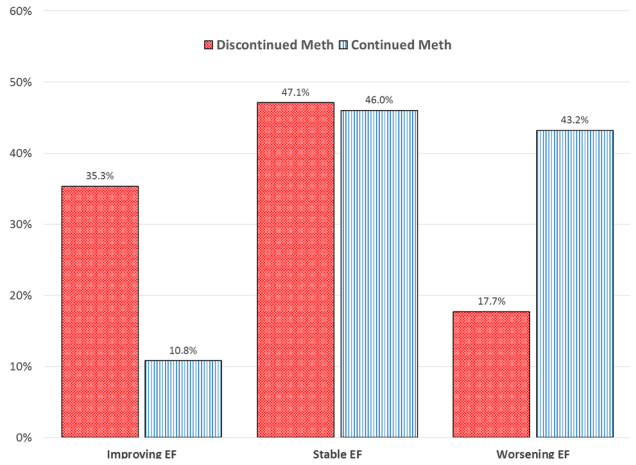

Fig. 2 Overall p value for EF trajectory versus methamphetamine use 0.06 (Fisher's exact test). p value for comparing % EF trajectory improving by meth trajectory (i.e., 35.3 % EF improved in those with an improving meth trajectory versus 10.8 % EF improved in those with a continued meth trajectory): 0.05 (Fisher's exact test). p value for comparing % EF trajectory worsening by meth trajectory (i.e., 17.7 % EF worsening in those with improving meth trajectory versus 43.2 % EF worsening in those with continued meth trajectory): 0.12 (Fisher's exact test)

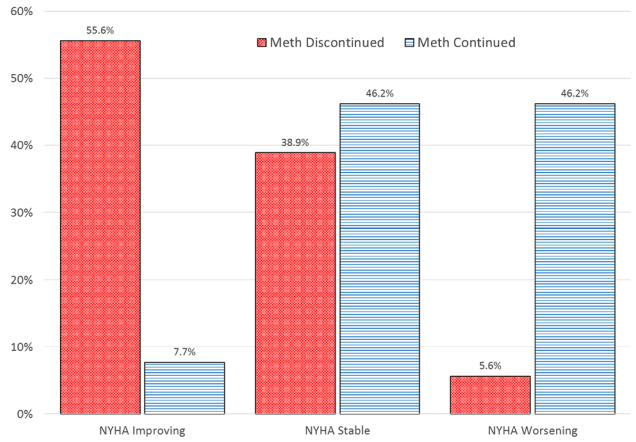

Fig. 3 Overall p value <0.001 for NYHA trajectory versus methamphetamine use (Fisher's exact test). p value for comparing % NYHA trajectory improving by meth trajectory (excluding fluctuating) (i.e., 55.6 % NYHA improved in those with an improving meth trajectory versus 7.7 % NYHA improved in those with a continued meth trajectory): <0.001 (Fisher's exact test). p value for comparing % NYHA trajectory worsening by meth trajectory (excluding fluctuating) (i.e., 5.6 % NYHA worsening in those with an improving meth trajectory versus 45.0 % NYHA worsening improved in those with a continued meth trajectory): 0.003 (Fisher's exact test)

Table 4 NYHA trajectory by meth trajectory ($n = 61$ with data for both)

Meth trajectory	NYHA trajectory n (% of row)		
	Improving	Stable	Worsening
Discontinued ($n = 18$)	10 (55.6)	7 (38.9)	1 (5.6)
Continued ($n = 39$)	3 (7.7)	18 (46.2)	18 (46.2)

Overall p value (for 2 × 3 table): <0.001 (Fisher's exact test)

p value for comparing % NYHA trajectory improving by meth trajectory (excluding fluctuating) (i.e., 55.6 % NYHA improved in those with an improving meth trajectory versus 7.7 % NYHA improved in those with a continued meth trajectory): <0.001 (Fisher's exact test)

p value for comparing % NYHA trajectory worsening by meth trajectory (excluding fluctuating) (i.e., 5.6 % NYHA worsening in those with an improving meth trajectory versus 46.2 % NYHA worsening improved in those with a continued meth trajectory): 0.003 (Fisher's exact test)

of a clear association between methamphetamines and cardiomyopathy [2, 7, 11, 19]. Heart failure is responsible for over one million hospital admissions annually in the USA [5]. A large multicenter study showed that approximately 5 % of patients admitted for acute decompensated heart failure self-reported illicit stimulant abuse [7]. These patients were also shown to have significantly lower ejection fractions and more likely to have multiple hospital readmissions [7]. In addition, because of deficiency of resources, ongoing substance abuse and noncompliance, this patient population presents a challenge to the treating clinician. There is a lack of data on compliance with evidence-based therapy for systolic congestive heart failure in methamphetamine abusers with CHF. However, methamphetamine abusers with HIV have been shown to have poor adherence to antiretroviral therapy [20].

The pathogenesis of methamphetamine-associated cardiomyopathy is complex and likely multifactorial. Moreover, methamphetamine likely interacts with underlying pathology, such as intrinsic coronary artery disease. Direct toxic effects, catecholamine excess, vasospasm, ischemia, reactive oxygen species and mitochondrial injury have all been proposed mechanisms for myocardial injury [21, 22]. Catecholamines are thought to cause cardiac changes by increasing oxygen consumption. The cardiac workload is increased. In addition, oxygen wasting occurs due to uncoupling of oxidative phosphorylation [23]. Case studies and autopsy reports have shown global coronary microvascular vasospasm and diffuse myocardial ischemia likely associated with catecholamine excess in methamphetamine abusers [9, 24]. Necrosis, fibrosis, hypertrophy and cardiac enlargement, all indicators of catecholamine toxicity, have been found in methamphetamine abusers on autopsy [19]. Methamphetamine-associated histological changes include extensive myocardial remodeling with perivascular and interstitial fibrosis, myocyte destruction with proliferation of fibromyocytes, cellular vacuolization, patchy cellular infiltration, eosinophilic degeneration and edema [23, 25]. Contraction band necrosis has been shown to be a prominent finding in cases of cocaine-related sudden death as well as methamphetamine use [2, 26]. The authors suggested that catecholamine excess from cocaine

use contributed to the contraction band necrosis, leading to risk of ventricular arrhythmia. It was also suggested that fibrosis may be caused by healed contraction band necrosis [26], which may also play a role in methamphetamine-associated myocyte fibrosis.

Gradual reversal of the cardiac lesions has been shown in animal models after methamphetamine withdrawal [23]. It has been postulated that fibrosis and granulation tissue form from chronic eosinophilic degeneration and myolysis. However, the remaining myocardium is able to recover [23]. The use of cardiovascular magnetic resonance with late gadolinium enhancement has been reported to be useful in identifying irreversible cardiac damage by the presence of myocardial fibrosis [27]. A case of severe methamphetamine-associated cardiomyopathy with the absence of macroscopic regions of fibrosis showed complete recovery at 6 months [27]. Therefore, the absence of late gadolinium enhancement may be used as a way to predict recovery in methamphetamine abusers [27]. A small proportion (9.2 %) of our patients with MAC presented with heart failure with preserved ejection fraction. This number was lower than prior studies published from which we have found that the prevalence of preserved ejection fraction among patients with heart failure ranged from 40 to 71 %, with a mean of 54 % [28].

Our results show that there was a nonsignificant trend toward correlation between methamphetamine use over time and EF and significant correlation between methamphetamine use over time and NYHA functional class. This is likely due to development of myocardial fibrosis in chronic methamphetamine users over time, which, even after cessation of methamphetamine use, becomes irreversible. We hypothesize that the myocardial dysfunction may be reversible if methamphetamine use is discontinued prior to formation of significant fibrosis.

Limitations

Our study population, which was based in southern California, showed a majority of Caucasian patients but also a large number of African-American and Hispanic patients. The patient characteristics and findings of our study may not be representative of hospitals in other geographic and socioeconomic settings. However, our patient mix does represent an urban population typically enrolled in similar studies of drug abuse. A large multicenter national database study showed patients with heart failure and self-reported illicit drug use to be young, more likely to be male and more likely to be African-American [7]. Our population was not referred and admitted through our emergency room and not associated with drug rehabilitation centers.

As with all retrospective studies, there are inherent limitations. We were reliant on the documentation by other physicians for details of drug abuse, history of confounding factors and symptoms regarding functional class, as well as the patient's ability to relay accurate information. We assume this documentation is accurate and drug toxicology screens were also available to appropriately group patients as methamphetamine abusers. We cannot say with certainty that all cases of MAC were represented, making it difficult to identify the entire exposed cohort. There may have been methamphetamine abusers who were treated for acute decompensated heart failure where a drug toxicology screening was not ordered and the patient was not truthful about their drug history, thereby underestimating the true prevalence of MAC. Patients receive care at multiple hospitals; therefore, our records may not represent their complete history. Frequency and duration of methamphetamine abuse were collected when possible, but were not available for all patients, largely due to lack of data. However, in general, our population seeks care locally and therefore often presents to the same hospital. The hospital site is the largest in San Diego. Unlike alcohol and cocaine, there has been shown to be false-positive methamphetamine urine drug screen from commonly prescribed medications including cough suppressants and decongestants [29]. However, our population was followed over time, and many patients had multiple positive drug screens and self-reported methamphetamine abuse, which would tend to exclude those in the cohort who were not actually methamphetamine abusers.

A large limitation is the possibility of noncompliance with evidence-based therapy for systolic congestive heart failure. This would likely track along with continued meth use. We were unable to track compliance. Admission to the hospital is almost always associated with a decline in NYHA class, so there is a potential bias, in that those who were abstinent and therefore got better would less likely be counted in the study, as they would not have been admitted. Nonetheless, by assessing admissions for noncardiac complaints, we were still able to record a significant number of patients (20 %) who had become abstinent and improved their status.

Conclusions

There was a significant increase in the prevalence of MAC during the study period for all CHF admissions in our hospital system. Continued methamphetamine use is associated with worsening clinical markers of cardiomyopathy severity including declining EF and functional status, while cessation of methamphetamine is associated with improvement in functional status and a trend toward correlation for improved EF.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest or disclosures to report.

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